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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/413,110	10/06/1999	EVAN C. UNGER	UNGR-1580	1596

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/413,110	UNGER, EVAN C.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116-184* is/are pending in the application.

4a) Of the above claim(s) *132-137,142-145,152-159,161-163,167 and 175-177* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116-131, 138-141, 146-151,160,164-166, 168-174, and 178-184* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed on August 10, 2004 has been entered. Claims 116-184 are pending. This Application contains claims 132-137, 142-145, 152-159, 161-163, 167, 175-177 drawn to nonelected species. Claims 116-131, 138-141, 146-151,160,164-166, 168-174, and 178-184 read on the elected species and have been acted on merits. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any rejection that is not addressed in this Office Action is considered obviated in view of the Amendment and the presented arguments.

2. The effective priority date of this Application is June 19, 1996 because the parent application SN 08/666129, now Patent 6,033,645 has described effective ultrasonic energy for delivery of bioactive agents in col. 5, lines 28-29; col. 7, lines 37-49, and col. 41-42.

Response to Arguments

Applicant's arguments with respect to the following rejections have been fully considered and are addressed accordingly with each rejection.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 116-131, 138-141, 146-151, 160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al US Patent 5,695,460.

Siegel discloses methods of utilizing an ultrasonic energy and an ultrasonic contrast agent containing perfluorinated microbubbles in combination with a

thrombolytic agent to treat vascular thrombosis, (abstract; col 2 lines 1-65; examples 1-5; col 14, lines 4-30). Siegel specifically disclose that the ultrasound may be applied intravascularly by means of a miniature ultrasonic transducer or by a guide wire for transmitting ultrasound directly into the vessel (col 2, lines 7-10). Siegel's preferred ultrasound contrast agent is Echogen which contains phospholipids and polyethylene glycol (col 5, lines 50-53). Siegel et al further indicate the use of other types of contrast agents such as gas filled liposomes, or gas filled microbubble for their thrombus lysing method (col 5, lines 30-48). Siegel administers his drugs to an area in proximity of a thrombosis, which by its nature is hypo-perfused.

The recitation of "increasing delivery of bioactive agents from the vasuclature" is viewed to be relative to an intravenous delivery process of a bioactive agent wherein no ultrasound energy is employed. Since Siegel employs at least some level of localized ultrasound energy, his process is deemed to increase delivery of a bioactive agent, because it has shown that at least in the case of thrombosis, bioactive agents are more effective when used in conjunction with a gaseous contrast agent and external ultrasound energy.

In order to assert their clinical benefits, bioactive agents administered intravenously must go through the vessel walls. In another words, absorption occurs through the vasuclature structure. It is well established in the art that blood vessels are composed of three cellular layers, and at least one of such layers, *Tunica Intima*, include endothelium cells that lines the lumen of all vessels. Such endothelium layer

allows absorption of molecules through the vessel walls.[1] Therefore, such functional outcome is inherent to the process of administering drug intravenously.

Siegel fails to explicitly teach the instantly claimed infusion rates or ultrasound frequencies. Nevertheless, it would have been obvious to one of ordinary skill in the art to optimize the rate of infusion and the ultrasound frequencies by routine experimentation, because the ordinary skill in the art would have had a reasonable expectation to succeed in enhancing the lysis of a vessel thrombus when optimizing such parameters. Changes in rate of administration or ultrasound frequencies will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such rate of administration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

4. Applicant's arguments with respect to this rejection have been fully considered but are not persuasive. Applicant first argues that Siegel's teachings are in direct contradiction of the instant claims. Applicant concludes that there would have been not motivation to modify the Siegel reference towards the instant claims. (see Arguments at page 14).

In response, Examiner that Siegel's teachings are not a direct teaching away from the instant claims. Thus, Applicant's conclusion is not correct. Here, Applicant appears to misinterpret what it means to "teach away" from a patented invention. Generally, "disclosed examples and preferred embodiments do not constitute a teaching

[1] See fn 1 of the Last Office Action dated 6/16/2004, Absorption and distribution of Drugs, at pages 91-92

which is away from a broader disclosure or nonpreferred embodiments." *In re Susi*, 169 USPQ 423 (CCPA 1971). "In general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the results sought by the applicant." *In re Gurley,* 31 USPQ2d 1130, 1131-2 (Fed. Cir. 1994). Here, the mere fact that there is an alternative means of improving drug delivery as described by Siegel does not preclude optimization of ultrasound frequencies or infusion rates that is obvious over Siegel.

Specifically, the portions of Siegel patents that Applicant characterizes as a "teaching away" (col 5, lines 29-31, 59-60) does not discourage one of ordinary skill in the art to employ the frequencies instantly claimed. Siegel at col 5, lines 29-31 states that it has been found that when ultrasound is applied at a lower, rather than a higher frequency, the effectiveness of the method is markedly enhanced. First, the recitations "higher frequencies" does not teach against the instantly claimed ranges. In fact such recitation is relative and viewed to be open for optimization. One of ordinary skill in the art would have most likely performed further experimentation to determine what is the highest range of ultrasound frequencies capable of producing the same results described in Siegel.

Second, Applicant has not provided any evidence or explain how the disclosures of the prior art show that their claimed invention is unlikely to be productive of Siegel's desired result, when Siegel in fact introduces the concept of employing ultrasound to improve cavitation of contrast microbubbles to improve drug delivery and the final

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obtained from the website, ~~druglibrary.org/schaffer/ library/studies/ledain,~~ Last visited on June 10, 2004

clinical outcome. Simply, there is no statement in Siegel showing that the instantly claimed ultrasound frequencies would have been a less attractive range for drug delivery. Therefore, Examiner concludes that a person of one ordinary skill, upon reading the Siegel's reference, would not have been discouraged from optimizing the path set out by Siegel, or would have taken a direction divergent from the path that was taken by the applicant. Thus, since Siegel clearly teaches the method steps of the instant claims, modifying the ultrasound frequencies or the rate of infusion would have been achieved by routine experimentation.

Applicant further argues that Siegel never teaches the use of perfluorocarbon gas as recited in claim 141. (see Arguments at page 14). This argument is not persuasive, because no unexpected results have been presented. Examiner states that Siegel clearly envisioned the concept using stabilized gas bubbles (i.e. gaseous liposomes). (see col 14, line 28-30). Siegel used a perfluorocarbon that is gaseous at body temperature; thus, it is viewed to be a functional equivalent of the gases instantly claimed in claim 141. Applicant has not provided any evidence showing that indeed the gases of claim 141 provide unexpected results. Thus, Applicant's arguments are not persuasive.

5. Claims 116-131, 138-141, 146-151, 160,164-166, 168-174, and 178-184 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al US Patent 5,695,460 in view of Porter US Patent 5,648,098.

Applicant's arguments with respect to this rejection have been fully considered but are not found persusuve. Applicant argues that Siegel teaches away from using the instantly claimed ultrasound frequencies and thus it cannot be combined with Porter.

For reasons set forth above, Siegel does not "teach away" from the frequencies claimed here. In fact Porter shows that the state of art does not discourage the use of instantly claimed ultrasound frequencies for drug delivery. (see col 4, lines 48-50). Thus, their combined teachings would have rendered the instant claims obvious, because one of ordinary skill in the art would have had a reasonable expectation to succeed in optimizing the rate of administration or ultrasound frequencies to improve availability of contrast agents and the end clinical outcome.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action because the scope of the claims have been modified. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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